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25 January 1960

Dr. Rudolf Bircher
Sandoz Pharmaceuticals
Sandoz, Inc.
Hanover, New Jersey

Dear Dr. Bircher:

We have finally completed our study on tolerance to psilocybin and LSD-25 and cross-tolerance between these drugs in five subjects, supplementing the earlier study of Dr. Isbell on five other subjects. The tables enclosed represent the combined data on all ten subjects.

As you will note in Table 3, there is no doubt that our subjects developed tolerance to LSD-25 (1.5 mcg/kg), and after they became tolerant to this drug, they exhibited cross-tolerance to psilocybin (150 mcg/kg), with respect to all measures except possibly the temperature-elevating effect of the latter drug. On the other hand, the evidence for development of tolerance to psilocybin is not so complete (althoughly strongly suggestive), and on several measures (temperature, blood pressure and knee jerk), the subjects remained reactive to LSD-25, after chronic administration of psilocybin for seven days.

One possible reason for the failure to demonstrate tolerance to psilocybin and cross-tolerance to LSD-25 on all measures is suggested by the data in Table 1 which indicate that, at least with respect to their effects on pupillary size and responses to questionnaire, the maximal doses of LSD-25 and psilocybin we used were not equipotent -- i.e., LSD-25 (1.5 mcg/kg) produced greater effects than psilocybin (150 mcg/kg), and/or, the period of chronic administration of psilocybin was too short.

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Since the question of tolerance and cross-tolerance in regard to psilocybin and LSD-25 is of considerable theoretical significance, we are thinking of doing another study, with larger doses of psilocybin (possibly up to 250 mcg/kg, maximal dose) and longer duration of chronic intoxication (14 days). To do this in the few months I still have remaining before my prospective sabbatical year abroad, we will have to use ten new subjects and begin the study within two weeks at the latest. Also, we have calculated that in addition to what we have left of the supply of psilocybin you so kindly furnished a few months ago, we would require about 2.0 grams for completion of the experiment.

Unfortunately, we cannot begin the experiment until we have the complete supply of psilocybin on hand, since we must do some preliminary assays of relative potency before committing ourselves to such a long and complicated experimental design. Therefore, the decision whether or not to undertake the new study depends on the possibility of your being able to send us 2.0 grams of psilocybin within the next two weeks.

I realize that this is an extraordinary request and that you may not have that much psilocybin on hand. However, I shall be very grateful if you will let me know as soon as possible what the prospects are.

With many thanks for your assistance, past and present, and with cordial regards,

Sincerely,

Abraham Wikler, M.D.
Acting Director

AW:bws

Enclosures

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Table I

Differences in Response to Control Doses of LSD and Psilocybin

MEASURE	DIFFERENCE IN RESPONSE
Temperature	- 0.31 ± 0.48
Pulse Rate	+27.55 ± 13.52
Blood Pressure	+34.75 ± 16.23
Pupillary Size	+ 4.54 ± 1.03***
Knee Jerk	+ 8.47 ± 22.40
Responses on Questionnaire	+39.25 ± 12.30**
Clinical Grade	+ 0.35 ± 0.25

Figures represent mean differences ± standard errors of the differences between means of responses to <u>two</u> control doses of LSD-25 (1.5 mcg/kg) and means of responses to <u>two</u> control doses of Psilocybin (150 mcg/kg).

Note: ** = $P < .02$

*** = $P < .01$

+, indicates LSD-25 stronger in effect than Psilocybin

-, indicates Psilocybin stronger in effect than LSD-25

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Table 2

Differences in Responses to Placebo, 1.5 mcg/kg of LSD-25, and 150 mcg/kg of Psilocybin on first and second controls.

	DRUG		
MEASURE	Placebo	LSD-25	Psilocybin
Temperature	+ 0.98 ± 0.63	+ 0.42 ± 0.64	- 1.24 ± 0.53*
Pulse Rate	-11.53 ± 13.30	-12.62 ± 18.40	-19.60 ± 9.30
Blood Pressure	- 1.10 ± 15.70	- 1.35 ± 12.70	-25.40 ± 11.60
Pupillary Size	- 0.29 ± 1.65	+ 0.52 ± 1.18	+ 0.10 ± 0.83
Knee Jerk	-12.56 ± 11.90	-14.83 ± 21.75	+17.88 ± 18.70
Responses on Questionnaire	+ 0.90 ± 1.31	+ 0.60 ± 6.10	+ 4.90 ± 9.65
Clinical Grade	+ 0.10 ± 0.10	- 0.30 ± 0.20	+ 0.20 ± 0.41

Figures represent the mean differences ± standard errors of the differences between measurements on the first and second controls in 10 subjects. None of the differences except that for temperature change after psilocybin were significant.

+, Indicates that the average measurement was increased on the second control,

-, Indicates that it was decreased.

* = $P < .05$

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Table 3

Differences between Control Response to LSD-25 and Psilocybin and Response after Chronic Administration of either Drug.

Measure	After LSD Chronically		After Psilocybin Chronically	
	LSD ("Direct" Tolerance)	Psilocybin ("Cross" Tolerance)	Psilocybin ("Direct" Tolerance)	LSD ("Cross" Tolerance)
›erature	- 1.93 ± 0.79*	1) - 1.85 ± 0.61**	1) - 1.87 ± 0.47***	- 0.50 ± 0.59
		2) - 0.62 ± 0.67	2) - 0.63 ± 0.47	
Pulse Rate	-47.70 ± 8.45***	-17.05 ± 16.60	-22.20 ± 11.90[a]	-33.05 ± 10.41**
Blood Pressure	-79.80 ± 15.75***	-30.75 ± 7.33***	-33.55 ± 10.15***	-23.70 ± 15.30
Pupillary Size	-11.75 ± 1.67***	- 5.77 ± 1.58***	- 3.17 ± 1.20*	- 4.72 ± 1.45***
Knee Jerk	-71.16 ± 23.55**	-67.84 ± 16.97***	-52.69 ± 10.03***	-41.79 ± 19.51[a]
Responses on Questionnaire	-63.00 ± 18.14***	-21.85 ± 5.52***	-16.95 ± 7.69[b]	-57.10 ± 19.20**
Clinical Grade	- 1.65 ± 0.32***	- 1.35 ± 0.17***	- 0.95 ± 0.23***	- 1.40 ± 0.32***

... e: 1, Indicates differences obtained, using first control values,
2, Indicates differences obtained, using second control values

Figures represent the mean differences ± standard errors between the average of the two controls (with the exception of 1 and 2 which were significantly different) and the values found when patient was tested with LSD-25 or psilocybin after receiving either drug chronically

* , = P < .05
** , = P < .02
***, = P < .01

a, = P > .05, < .10
b, = t = 2.20
(at t = 2.26, P = .05)